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REVIEW ARTICLE

High-Risk Populations Identified in Childhood Cancer Survivor Study Investigations: Implications for Risk-Based Surveillance

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ABSTRACT

Childhood cancer survivors often experience complications related to cancer and its treatment that may adversely affect quality of life and increase the risk of premature death. The purpose of this manuscript is to review how data derived from Childhood Cancer Survivor Study (CCSS) investigations have facilitated identification of childhood cancer survivor populations at high risk for specific organ toxicity and secondary carcinogenesis and how this has informed clinical screening practices. Articles previously published that used the resource of the CCSS to identify risk factors for specific organ toxicity and subsequent cancers were reviewed and results summarized. CCSS investigations have characterized specific groups to be at highest risk of morbidity related to endocrine and reproductive dysfunction, pulmonary toxicity, cerebrovascular injury, neurologic and neurosensory sequelae, and subsequent neoplasms. Factors influencing risk for specific outcomes related to the individual survivor (eg, sex, race/ethnicity, age at diagnosis, attained age), sociodemographic status (eg, education, household income, health insurance) and cancer history (eg, diagnosis, treatment, time from diagnosis) have been consistently identified. These CCSS investigations that clarify risk for treatment complications related to specific treatment modalities, cumulative dose exposures, and sociodemographic factors identify profiles of survivors at high risk for cancer-related morbidity who deserve heightened surveillance to optimize outcomes after treatment for childhood cancer.

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INTRODUCTION

Childhood Cancer Survivor Study (CCSS) investigations have played an important role in characterizing long-term morbidity and mortality associated with childhood cancer treatment. Remarkably, for most outcomes studied, survivors exhibit impressive resilience and serious life-threatening morbidity is limited to a minority of survivors. However, as a whole, chronic health conditions, functional impairment, activity limitations, and psychosocial dysfunction are reported more commonly by childhood cancer survivors compared with siblings or age-matched population controls.[1-4] It is well established that the health consequences of cancer can negatively impact quality of life and predispose to premature death.[2,5]

Comprehensive ascertainment of host- and cancer-related factors in CCSS cohort participants has facilitated identification of specific groups at highest risk of morbidity who may benefit from risk-based surveillance. Factors influencing risk for specific outcomes related to the individual survivor (eg, sex, race/ethnicity, age at diagnosis, attained age), sociodemographic status (eg, education, household income, health insurance) and cancer history (eg, diagnosis, treatment, time from diagnosis) have been consistently investigated. This approach has enabled CCSS investigators to clarify risk for previously described outcomes in relation to specific treatment modalities and cumulative dose exposure and identify novel health outcomes important to providers monitoring long-term survivors. For example, the CCSS investigation evaluating overall physical morbidity in relation to cancer type and therapy in 10,397 adults surviving childhood cancer demonstrated that exposure to one of five specific treatment combinations (chest radiation plus bleomycin, chest radiation plus anthracycline, chest radiation plus abdominal or pelvic radiation, anthracycline plus an alkylating agent, and abdominal or pelvic radiation plus an alkylating agent) was associated with at least a 10-fold excess risk of having a severe or life-threatening chronic health condition.[4] Individually, these modalities confer excess risk for a variety of adverse health

outcomes including cardiopulmonary disease and secondary carcinogenesis, which are already significant health issues for an aging population. Treatment with alkylating agents or abdominal/pelvic radiation predispose to a risk of gonadal and germ cell dysfunction that is influence by cumulative dose, sex, and age at treatment. Treatment with a combination of these modalities produces a group at highest risk for gonadal failure and infertility.[6,7] As the estimated cumulative incidence of chronic health conditions reported by the cohort increased with more prolonged time from cancer diagnosis, CCSS study results provide important information for clinicians caring for aging adults treated for cancer during childhood who may be at greater risk for morbidity.[4] The objective of this manuscript is to review how data derived from CCSS investigations have facilitated identification of childhood cancer survivor populations at high risk for specific organ toxicity and subsequent cancers and how this has informed clinical screening practices. Table 1 summarizes the host and treatment factors increasing the risk of selected medical complications 5 or more years after diagnosis after childhood cancer that are discussed in the sections that follow.

ENDOCRINE AND REPRODUCTIVE FUNCTION

Thyroid Abnormalities

Thyroid abnormalities are commonly reported in survivors of childhood cancer, particularly those treated with radiation therapy (RT), but the true prevalence of these problems has been difficult to establish because of the relatively short follow-up time of most prior studies. Moreover, the small sample size of the majority of published studies precluded elucidation of the potential interactions between patient and treatment variables in the genesis of thyroid disease. The CCSS cohort's large sample size allowed for characterization of risk factors for thyroid disease among survivors of Hodgkin's disease (HD).[8] Increasing radiation dose, female sex, and older age at diagnosis were major risk factors for an underactive thyroid in the 28% of HD survivors with this condition.[8] The actuarial risk of hypothyroidism 20 years from diagnosis was 30% among HD survivors who received 35 to 44.99 Gy and 50% over ≥ 45 Gy. The relationship between increasing radiation dose and risk for hypothyroidism has been previously reported.[9,10] However, the impact of age at diagnosis on risk for hypothyroidism has been confounded by the fact that older patients were more likely to be treated with higher doses of radiation. Among HD survivors in the CCSS cohort, those older than 15 years of age at diagnosis were at increased risk of developing hypothyroidism compared with younger patients (relative risk [RR] 1.5; 95% CI, 1.2 to 1.9). This investigation was also the first pediatric series to identify female sex as a risk factor for radiation-induced hypothyroidism (RR 1.7; 95% CI, 1.4 to 2.1).

This study also evaluated risk factors for hyperthyroidism and thyroid nodules. Hyperthyroidism was noted among 5% of HD survivors in the CCSS, which represents an eight-fold (95% CI, 4.6 to 15.1) greater risk compared with the sibling group.[8] Survivors with neck radiation doses ≥ 35 Gy were at higher risk (RR 2.2; 95% CI, 1.2 to 4.7) compared with those treated with lower doses. Evaluation of risk factors for the development of thyroid nodules among HD survivors indicated that sex, radiation dose, and time from diagnosis significantly influenced risk. HD survivors more likely to develop nodules were female (RR 4.0; 95%, CI 2.5 to 6.7), had received ≥ 25 Gy (RR 2.9; 95% CI, 1.4 to 6.9), and were more than 10 years from diagnosis (RR 4.8; 95% CI, 3.0 to 7.8).

Implications for Risk-Based Screening for Thyroid Disease

The prevalence of thyroid disease in childhood cancer survivors treated with radiation impacting the thyroid gland warrants annual monitoring of thyroid function; more frequent follow-up may be indicated for children during rapid growth. Because thyroid function can have significant impact on general health (eg, growth, reproduction, metabolism, cardiovascular and neurocognitive function, and emotional health), at-risk survivors should be educated about the signs and symptoms of hypo- and hyperthyroidism. Thyroid abnormalities may present years after radiation when survivors have transitioned back to their primary care providers. This underscores the

Table 1. Host and Treatment Factors Increasing Risk of Selected Medical Complications ≥ 5 Years After Diagnosis of Childhood Cancer

Medical Late Effect	Host Factor	Treatment Factor
Hypothyroidism[8]	Female; older age at diagnosis (> 15 years)	Radiation to thyroid, any dose, increasing risk with increasing dose
Hyperthyroidism[8]	Time since diagnosis < 3 years	Radiation to thyroid ≥ 35 Gy
Thyroid nodules[8]	Female; time since diagnosis > 10 years	Radiation to thyroid ≥ 25 Gy
Short stature (analysis limited to ALL survivors)[13]	Female; diagnosis before puberty	Cranial radiation > 20 Gy; radiation to spine
Short stature (analysis limited to brain tumor survivors)[12]	Younger age at diagnosis (< 4 years)	Radiation to hypothalamic pituitary axis, any dose, increasing risk with increasing dose
Overweight/obese[15]	Female; younger age at diagnosis	Cranial radiation
Acute ovarian failure[6]	Diagnosis ≥ 12 years	Ovarian radiation > 10 Gy; procarbazine and cyclophosphamide
Premature menopause[7]	Older attained age	Ovarian radiation; alkylating agents
Pulmonary fibrosis[25]		Chest radiation; cyclophosphamide, bleomycin, busulfan, CCNU, and BCNU
Stroke[31,32]	Smoking (Hodgkin's disease)	Mantle radiation > 40 Gy for Hodgkin's disease; cranial radiation > 30 Gy for brain tumor and leukemia
Motor problems[34]		Radiation > 50 Gy to frontal regions
Hearing loss[34]		Radiation > 50 Gy to posterior fossa
Seizure disorder [34]		Radiation dose > 30 Gy to any cortical segment of brain

Abbreviations: ALL, acute lymphoblastic leukemia; CCNU, lomustine; BCNU, carmustine.

importance of educating providers about the need for regular assessment of thyroid gland function by clinical history, physical examination, and laboratory evaluation. Clinical history suggesting thyroid dysregulation, evaluation of growth and pubertal development, palpation of the thyroid gland, and measurement of thyroid stimulating hormone and free thyroxine levels should be used to determine the need for further laboratory and imaging studies or referral to an endocrinologist. The time to onset of specific thyroid complications should be considered. For example, the majority of thyroid nodules have an indolent course with presentation many years after radiation. Since thyroid nodules do not uniformly undergo malignant transformation, ultrasonography and fine needle aspiration should be reserved only for those with suspicious clinical symptoms or palpable abnormalities.[11]

Linear Growth and Adult Stature

Growth and development can be significantly affected by childhood cancer therapy. CCSS participants most at risk include CNS tumor and leukemia survivors, particularly those treated with craniospinal RT. Gurney et al[12] analyzed 921 brain tumor survivors, mean age 27 years (range, 20 to 45 years), and found nearly 40% to be below the 10th percentile for height. Mean male height was 1.69 m (SD = 0.12) compared with 1.79 m ($P < .001$) among age-matched males in the National Health Interview Study (NHIS); mean female height was 1.58 m (SD = 0.11) compared with 1.65 m ($P < .001$) among NHIS females. Significant risk factors included earlier age at diagnosis and higher doses of RT to the hypothalamic-pituitary axis. A similar analysis found a decrease of attained adult height among 2,434 acute lymphoblastic leukemia (ALL) survivors.[13] Significant risk factors included female sex, diagnosis before puberty, higher doses of cranial RT (≥ 20 *v* < 20 Gy), and RT to the spine.

Weight and Body Mass Index

In addition to concerns about attained height, alterations in weight and body mass index (BMI) can have significant impacts on long-term health of childhood cancer survivors. Several analyses from the CCSS cohort have identified survivors at risk of being over- or underweight.[12,14-16] Similar to other studies, those exposed to RT, particularly survivors of ALL, are at increased risk of being overweight or obese. Among CNS tumor survivors, the BMI distribution did not significantly differ from NHIS normative values.[12] In contrast, Oeffinger et al[16] found an increased risk of being overweight (BMI, 25.0 to 29.9) and obese (BMI ≥ 30.0 kg/m^2) among adult ($\geq$18 years) survivors of ALL. The risk of overweight/obesity was greatest in female survivors treated with cranial radiation before age 10 years.

Implications for Risk-Based Screening of Growth and BMI

Exposure to cranial irradiation for childhood cancer is associated with impairment of linear growth, alterations in pubertal timing, and metabolic dysregulation that predisposes to short stature and overweight. Female survivors and those treated at younger ages ($<$ 4 years of age) are at greatest risk of these complications. Close monitoring of growth and development is necessary as these children mature to facilitate timely referral for hormonal therapy that can optimize achievement of adult height. Nutritional status and thyroid function should be evaluated in any poorly growing child. Anticipatory guidance regarding the benefits of healthy dietary habits and regular physical activity should be provided to all survivors, especially those who are overweight or obese.

Adult growth hormone (GH) deficiency has been documented in select groups of childhood cancer survivors. The risks and benefits of GH replacement in survivors who have completed linear growth have been an area of some debate and a focus of ongoing research. Because untreated GH deficiency has been associated with cardiovascular disease risk factors linked to the metabolic syndrome, questions persist regarding the potential benefits of GH replacement among adults treated for cancer during childhood.[17] Survivors at risk of GH deficiency following hypothalamic-pituitary axis radiation should undergo periodic screening of fasting blood glucose, serum insulin, and lipid profile to identify opportunities for risk reduction through remediation of comorbid conditions that adversely impact cardiovascular health. Risk-based screening recommendations for potential endocrine toxicity associated with treatment for childhood cancer are summarized in Table 2.

Sexual Development

Issues of pubertal development, fertility, and pregnancy become significant concerns for survivors of childhood cancer as they mature. Gurney et al[14] reported a significant increased need for medically induced puberty among CCSS brain tumor survivors (RR = 86; 95% CI, 31 to 238), with the risk being higher among those treated with surgery, chemotherapy, and RT (RR = 1.8; 95% CI, 1.1 to 3.0) compared with those treated with surgery and RT. Chow et al[18] used menarche as a marker of puberty among 949 female ALL survivors. Early menarche ($<$ 10 years of age) was associated with both cranial (RR = 6.2; 95% CI, 2.1 to 18.5) and craniospinal RT (RR = 8.6; 95% CI, 1.9 to 38.6), while delayed menarche ($>$ 16 years of age) was associated only with craniospinal RT exposure (RR = 4.8; 95% CI, 1.4 to 16.7). No difference was found between less than 20 Gy and $\geq$ 20 Gy, suggesting risk begins at lower doses. Notably exposure to alkylating agents in this population, in which cumulative doses of alkylating agents were low, had no effect on timing of menarche.

Reproductive Function

Female survivors are also at risk of premature ovarian failure. Chemaitilly et al[6] analyzed the risk of ovarian failure occurring within 5 years of cancer diagnosis among 3,390 female survivors $\geq$ 18 years old. Those with a history of hypothalamic/pituitary tumors, treatment with more than 30 Gy cranial RT, and bilateral oophorectomy were excluded. Survivors who were older at diagnosis ($>$ age 12 years of age) and those treated with ovarian radiation doses more than 10 Gy had the highest risk of developing acute ovarian failure. In another CCSS investigation, for women who continued to menstruate for at least the first 5 years postdiagnosis, nonsurgical premature menopause was identified in 8% (RR = 13.2; 95% CI, 3.3 to 53.5) compared with siblings.[7] Increasing dose of ovarian RT and the combination of any ovarian RT plus alkylating agent exposure were associated with the greatest risk of premature menopause. Among childhood cancer survivors who become pregnant after treatment with most chemotherapeutic agents, significant adverse pregnancy outcomes have not been identified.[19] However, the offspring of women who received pelvic irradiation are at risk for low birth weight.

Table 2. Risk-Based Screening Recommendations for Potential Endocrine and Reproductive Organ Toxicity Associated With Treatment for Childhood Cancer

Affected Organ/Tissues	Treatment	Potential Late Effect	Risk-Based Screening
Hypothalamic-pituitary axis	Radiation impacting neuroendocrine axis	Growth hormone deficiency overweight/obesity	Tanner staging every 6 months until sexually mature; height, weight, BMI every 6 months until growth is completed, then yearly; fasting blood glucose and lipid profile every 2 years and more frequently if indicated; and consider evaluation for other co-morbid conditions including dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, and insulin resistance
Thyroid gland	Radiation impacting thyroid gland	Hypothyroidism; hyperthyroidism; thyroid nodules	Thyroid palpation yearly; consider ultrasound/ fine-needle aspirate for evaluation of palpable nodules
Female reproductive organs	Radiation impacting ovaries; alkylating agents*	Gonadal dysfunction (ovarian); delayed/arrested puberty; premature menopause; infertility	Tanner staging yearly; FSH, LH, estradiol baseline at age 13 years, and as clinically indicated in patients with delayed puberty, irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency; consider evaluation for conditions exacerbated by hypogonadism (eg, osteopenia/osteoporosis)
Male reproductive organs	Radiation impacting testes; alkylating agents*	Gonadal dysfunction (testicular); germ cell failure (oligospermia, azoospermia, infertility); leydig cell dysfunction; delayed/arrested puberty (hypogonadism)	Testicular volume by Prader orchidometry yearly until sexually mature; FSH, LH, testosterone baseline at age 14 years, and as clinically indicated in patients with delayed puberty or clinical signs and symptoms of testosterone deficiency; consider evaluation for conditions exacerbated by hypogonadism (eg, low bone mineral density)
Skeleton	Corticosteroids, methotrexate	Low bone mineral density	Bone density evaluation (DXA or quantitative CT) baseline at entry into long-term follow-up, then repeat as clinically indicated)

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; DXA, dual energy x-ray absorptiometry; CT, computed tomography.
*Includes classical (busulfan, carmustine, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, procarbazine, thiotepa), heavy metal (carboplatin, cisplatin), and nonclassical (dacarbazine, temozolomide) alkylating agents.

Implications for Risk-Based Screening of Reproductive Function

Alkylating chemotherapy and RT to the gonads may cause ovarian dysfunction manifesting as delayed or arrested puberty, acute ovarian failure, premature menopause, and/or infertility. The risk of injury is related to the cumulative dose of these modalities and combinations including alkylating agents and abdominopelvic radiation. Risk-based assessment should be age appropriate, including Tanner staging, monitoring of pubertal progress and tempo, assessment of menstrual and pregnancy history, and close attention to clinical symptoms of menopause or sexual dysfunction. Baseline evaluation of hypothalamic pituitary gonadal axis function including follicle-stimulating hormone, luteinizing hormone, estradiol should be performed at age 13 years in females. These tests should be repeated as clinically indicated in survivors with pubertal delays, irregular menses, amenorrhea, and/or signs and symptoms of gonadal deficiency. Women at risk for early menopause should be counseled about the possible consequences of delaying childbearing since their reproductive years may be shortened. Conversely, those exposed to low cumulative doses of alkylating chemotherapy should be advised regarding the need for effective contraception if pregnancy is not desired. The impact of hypogonadism on linear growth and body composition should also be considered. Hormonal replacement therapy can optimize pubertal development and bone health, but its potential risks and benefits should be considered carefully in women at risk for secondary breast cancer after chest radiation. Obstetricians should be aware of the potential for pregnancy complications in women treated with abdominopelvic radiation for childhood cancer.[19] Risk-based screening recommendations for potential reproductive organ toxicity associated with treatment for childhood cancer are summarized in Table 2.

PULMONARY TOXICITY

Increased occurrence of pulmonary toxicity has been reported following treatment with dose-intensive protocols that include RT and/or high cumulative doses of chemotherapy among survivors of leukemia, rhabdomyosarcoma, and HD, and among individuals who undergo bone marrow transplantation.[20-24] The identification of these toxicities has resulted in substantial changes in treatment approaches, most strikingly for HD therapy. Although these treatment modalities are still a component of contemporary therapy, their use has been restricted to what are believed to be safe exposures. The large number of childhood cancer survivors in the CCSS cohort has made it possible to assess the overall and cumulative frequencies of the more common pulmonary conditions observed after cancer therapy, including pulmonary fibrosis, pulmonary insufficiency (defined by need for supplemental oxygen), chronic cough, and recurrent pneumonia.[25] Survivors treated with chest radiation were at highest risk for pulmonary toxicities; this group had a four-fold excess risk of lung fibrosis (RR = 4.3; 95% CI, 2.9 to 6.6) and two-fold excess risk of chronic pneumonia (RR = 2.2; 95% CI, 1.4 to 3.5). Treatment with busulfan (RR = 3.2; 95% CI, 1.5 to 7.0) and carmustine (RR = 2.1; 95% CI, 1.4 to 2.9) predicted a higher risk of pulmonary insufficiency. Evaluation of the prevalence of pulmonary complications in relationship to windows of time from diagnosis

demonstrated a peak prevalence during the time interval between diagnosis and end of therapy that declined in subsequent years.[25] The decline in prevalence of events suggested that the majority of survivors had a low likelihood of permanent pulmonary injury following acute events like infection or radiation pneumonitis, but the impact of aging and health behaviors on acute pulmonary injury remains to be established.

Implications for Risk-Based Screening of Pulmonary Function

Monitoring of pulmonary function during therapy permits early intervention with alternative strategies that can preserve pulmonary reserve. Symptomatic pulmonary dysfunction is uncommon in long-term survivors treated with contemporary therapy that proactively limits the doses of agents and modalities known to cause pulmonary injury. A baseline chest radiograph and pulmonary function testing including spirometry and diffusing capacity should be obtained in all survivors treated with bleomycin, busulfan, nitrosureas, or radiation volumes including the pulmonary parenchyma. Repeat assessments may be warranted in survivors with abnormalities of pulmonary function who are scheduled for general anesthesia. Counseling regarding abstinence from smoking or referral to smoking cessation programs is critical to reduce the risk of exacerbation of pulmonary dysfunction as well as tobacco-related cardiovascular disease and carcinogenesis.

CEREBROVASCULAR INJURY

Stroke is exceptionally rare among otherwise healthy young adults. Although several single institution reports have described small series of strokes among cancer survivors,[26-30] it has been difficult to determine the prevalence of stroke and risk factors for stroke among childhood cancer survivors. The large number of childhood cancer survivors in the CCSS cohort makes it possible to determine the rate and identify certain diagnostic risk groups as being at a relatively high risk of stroke with onset at greater than 5 years after cancer diagnosis.[31,32] Compared with the sibling control group, which had a similar rate of stroke to that reported among otherwise healthy adults, there was an increased relative risk of stroke among survivors of leukemia (RR = 6.4; 95% CI, 3.0 to 13.8), brain tumor (RR = 29; 95% CI, 13.8 to 60.7), and HD (RR = 4.32; 95% CI, 2.01 to 9.29).

RT is the most prominent treatment risk factor associated with subsequent stroke. Furthermore, RT treatment fields and doses appear to contribute to the risk.[31,32] For example, there was an increased relative risk of stroke among leukemia survivors treated with a dose of greater than 30 Gy cranial RT (RR = 7.74; 95% CI, 2.6 to 23.3) compared with leukemia survivors treated with no cranial RT or lower dose cranial RT. Also, there was an increased relative risk of stroke among brain tumor survivors treated with a dose of greater than 50 Gy cranial RT (RR = 3.3; 95% CI, 1.5 to 7.1) compared with brain tumor survivors treated without cranial RT. Among HD survivors who developed stroke, nearly all had received mantle radiation doses of 40 Gy.

Among leukemia survivors, there was an increased stroke risk among those who suffered relapse (RR = 21.6; 95% CI, 8.6 to 54.2).[31] Among brain tumor survivors, there was an increased relative risk of stroke after treatment with both cranial RT and alkylating agents (RR = 78.3; 95% CI, 35.1 to 174.5).[31] Both of these associations suggest an association with a relative increased intensity of therapy and need further investigation. Finally, among survivors of childhood HD, there was an increased risk of stroke if the cancer survivor reported smoking more than 10 cigarettes in their lifetime (RR = 3.37; 95% CI, 1.21 to 10.77). This is the first identified potentially modifiable risk factor for cerebrovascular disease among survivors of HD.

Implications for Risk-Based Screening of Cerebrovascular Disease

Head and neck radiation increases the risk for a variety of cerebrovascular complications including stroke, moyamoya, and occlusive vasculopathy. Among cohorts studied in the CCSS, radiation dose appears to significantly impact risk. Diagnostic groups most likely to present with cerebrovascular complications include survivors of brain tumors, leukemia, and HD. In most cases, a clinical presentation with motor and/or sensory deficits leads to neuroimaging that establishes the diagnosis. Consequently, risk-based surveillance should focus on history and neurological and neurocognitive assessment. Survivors at risk for extracranial vascular disease involving the carotid or subclavian vessels may have bruits or discrepant peripheral pulses on physical examination. Smoking is associated with a three-fold excess risk of stroke in HD survivors in the CCSS cohort, emphasizing the importance of promoting abstinence from smoking in this group.

NEUROLOGICAL AND NEUROSENSORY SEQUELAE

Survivors of childhood brain tumors are at risk of increased of late neurological and neurosensory morbidities as a result of combinations of the primary tumor and treatment with surgery, RT and chemotherapy.[33] Recognition of these adverse effects resulted in considerable efforts to modify therapy and reduce risk exposures to children with brain tumors to decrease their risk of late effects. Given the large number (n = 1,607) of brain tumor survivors in the cohort, the CCSS has considerable ability to define rates and risks of neurological and neurosensory sequelae. CCSS investigations have determined that survivors of childhood brain tumors have a high prevalence of neurological and neurosensory dysfunction (eg, hearing impairments, blindness, cataracts, and double vision), neurological dysfunction (eg, coordination and motor problems), and seizure disorder.[34] RT, RT treatment field, and RT dose appear to be associated with an increased relative risk of neurosensory and neurological sequelae.[34] RT exposure at greater than 50 Gy to the posterior fossa predicted a higher likelihood of developing any hearing impairment (RR = 3.7; 95% CI, 1.8 to 7.8). Children receiving at least 50 Gy to the frontal brain regions had a moderately elevated risk for motor problems (RR = 2.0; 95% CI, 1.0 to 3.9). Radiation dose of greater than 30 Gy to any cortical segment of the brain was associated with a two-fold elevated risk for a late seizure disorder.

This CCSS investigation also examined the time to onset of neurological and neurosensory dysfunction. Similar to the onset of pulmonary dysfunction, the majority of neurological and neurosensory dysfunction presented at diagnosis or during therapy, and demonstrated considerable decline in onset in the first and subsequent 5 years after diagnosis. Cataracts differed in this regard and occurred at a relatively constant rate of 1.7 to 2.2 per 1000 person years throughout

all time periods. Continued monitoring of the cohort will be important to evaluate the impact of aging on neurological and neurosensory sequelae predisposed by radiation and chemotherapy.

Implications for Risk-Based Screening for Neurological and Neurosensory Sequelae

Specific treatments for childhood cancer, especially those that directly impact nervous system structures, may result in sensory, motor, and neurocognitive deficits that may have adverse consequences on functional status, educational attainment, and future vocational opportunities. Survivors with primary malignancies involving neurological structures are particularly vulnerable to experiencing cancer-related neurotoxicity. Clinical manifestations may present early in the course of treatment, or become apparent later when the survivor fails to achieve anticipated developmental and educational expectations. Thorough documentation of motor, sensory, and neurocognitive deficits at diagnosis and periodic evaluation is essential to identify new or evolving neurotoxicity. Annual assessment of educational progress and referral for formal neuropsychological evaluation will facilitate identification of deficits and access to appropriate accommodations that can enhance opportunities for academic success. Neuropsychological evaluation should be repeated periodically as clinically indicated for patients with evidence of impaired educational or vocational progress since access to special education services has been demonstrated to have a positive impact on education achievement.[35]

SUBSEQUENT NEOPLASMS

A number of CCSS investigations have evaluated the epidemiology of subsequent neoplasms (SN) with the objective of characterizing risk profiles for secondary carcinogenesis.[8,36-46] This information is essential to guide modification of primary cancer therapies to decrease the risk of developing subsequent cancers in newly diagnosed patients. Survivor groups established to be at high risk for carcinogenesis can then be targeted for preventive strategies or interventions that facilitate early detection of subsequent cancers. In general, CCSS investigations have identified factors contributing to SN risk related to specific treatment exposures and diagnostic groups. Diagnostic groups exhibiting excess risk independent of treatment have been speculated to reflect genetic predisposition for carcinogenesis. Sex, age at treatment, and attained age also influence the subsequent risk of developing specific histological subtypes. This section summarizes key findings from CCSS publications that have clarified the relationships among host and treatment factors that contribute to an excess risk of subsequent carcinogenesis.

In the first CCSS investigation evaluating the incidence of and risk factors for SN, multivariable regression models adjusted for radiation exposure indicated that survivors at highest risk for the development of any SN were female ($P < .001$), diagnosed with cancer at a young age (P for trend $< .001$), had primary diagnosis of HD ($P < .001$) or soft tissue sarcoma ($P = .01$), and received treatment including alkylating agent chemotherapy (P for trend $= .02$).[41] The development of SNs of bone and soft tissues in survivors of primary sarcoma and subsequent CNS tumors in survivors of childhood leukemia or CNS tumors suggested that familial cancer predispositions may play a role in carcinogenesis. More detailed follow-up analyses of specific SN histological subtypes have disclosed novel relationships among SN risks related to primary diagnosis, age at diagnosis, attained age at SN diagnosis, and radiation dosimetry.[36,38,39,42] Table 3 summarizes host and treatment factors associated with an increased risk of selected subsequent neoplasms after childhood cancer.

Breast Cancer

Using multiple Poisson regression of standardized incidence ratios (SIRs) and adjusting for age at childhood cancer diagnosis, years of follow-up, and sex-specific change in risk of breast cancer with attained age, CCSS investigators determined that older age at childhood cancer diagnosis was not a statistically significant risk factor for breast cancer. This was not consistent with findings of previous investigations that reported a greater risk of breast cancer in girls treated with radiation between the ages of 10 and 16 years, presumably due to radiation delivery during a period of rapid breast tissue proliferation.[47,48] In the CCSS analysis of breast cancer incidence by primary cancer that was stratified by history of previous treatment with chest radiation, survivors of HD, bone sarcoma, soft tissue sarcoma, non-Hodgkin's lymphoma and Wilms tumor demonstrated an almost 25-fold excess risk of breast cancer (SIR = 24.7; 95% CI, 19.3 to 31.0) compared with the age-matched general population.[39] However, survivors of bone and soft tissue sarcomas who were not treated with chest RT also exhibited an increased breast cancer risk (SIR = 6.7 and

Table 3. Host and Treatment Factors Increasing Risk of Selected Subsequent Neoplasms After Childhood Cancer

Subsequent Cancer	Host Factor	Treatment Factor
Any subsequent malignancy histology[41]	Female sex, young age at diagnosis; primary diagnosis Hodgkin's disease or soft tissue sarcoma	Alkylating agents; epipodophyllotoxins; anthracyclines
Breast[39]	Female sex; primary diagnosis of bone tumor or soft tissue sarcoma	Chest radiation
Thyroid[8,45]	Younger age at diagnosis	Thyroid radiation (20 to 40 Gy)
CNS[42]	Young age at initial therapy (glioma); ≥ age 5 at initial therapy (meningioma)	CNS radiation
Sarcoma[38]	Primary diagnosis of soft tissue sarcoma; history of other subsequent neoplasm; family history of cancer	Radiation therapy; higher anthracycline dose (> 100 mg/m^2); higher alkylating agent dose (alkylators score ≥ 2)
Nonmelanoma skin cancer[43]	White race; older attained age; primary diagnosis of HD; family history of skin cancer	Radiation therapy

7.6, respectively), which suggested the presence of an hereditary cancer predisposition syndrome. In this group, breast cancer risk was independently associated with family history of sarcoma. The association of thyroid disease and excess breast cancer risk (RR = 1.7; 95% CI, 1.1 to 2.6) prompted investigators to propose thyroid disease as a potentially useful clinical marker for assessing breast cancer risk since both conditions reflected exposure to higher doses of radiation[8] or enhanced susceptibility to radiation toxicity.

Thyroid Cancer

Radiation to head and neck structures is a well-established risk factor for the development of a subsequent thyroid cancer; however, the magnitude of risk over the therapeutic dose range has not been well established. As part of a nested case-control study, CCSS investigators used novel radiobiological models to construct a radiation dose-response curve for thyroid cancer and evaluate patient and treatment characteristics on thyroid cancer risk.[44,45] Thyroid cancer risk increased with radiation doses up to 20 to 29 Gy (odds ratio [OR] = 9.8, 95% CI, 3.2 to 34.8), but decreased after childhood exposure to thyroid doses higher than 30 Gy consistent with a cell-killing effect. This fall in thyroid cancer risk at doses greater than 30 Gy remained, even when survivors of HD were excluded.[45] This investigation provided additional evidence of a diminished risk of subsequent thyroid cancer at radiation doses above 30 Gy and supported the carcinogenic effects of lower-dose radiation. Study findings also confirmed clinical observations that thyroid cancers are most likely to arise 10 years or later after a first malignancy in childhood and that radiation-associated risks for thyroid cancer remain elevated for at least 20 years from exposure, which have important implications for screening of at risk survivors.

CNS Tumors

Another case-control study conducted by CCSS investigators evaluated the dose-response relationships and modifying effects of host and treatment factors in survivors who developed SN of the CNS.[42] Children treated with therapeutic CNS radiation for a primary childhood malignancy are known to have an increased risk of subsequent CNS tumors.[49-52] However, our understanding of the magnitude of risk and details of the dose-response relationships over time have not been well defined, particularly for specific histological subtypes of CNS tumors. Modeling of excess relative risk following calculation of tumor site-specific radiation dosimetry disclosed an increased risk of subsequent glioma (OR = 6.78; 95% CI, 1.54 to 29.7) and meningioma (OR = 9.94; 95% CI, 2.17 to 45.6). In analyses evaluating the modification of radiation effect by host characteristics, excess relative risk per Gy for glioma was highest among children treated with radiation at age 5 years or younger, suggesting that susceptibility to radiation-related brain cancer decreases as brain development nears completion. The distribution of subsequent CNS tumors differed over time in relation to specific histological subtype. The risk of glioma was increased within 5 to 10 years after radiation, but declined to nearly background levels after 15 to 20 years. In contrast, the incidence of meningioma increased steadily after 5 to 10 years after radiation and showed no evidence of plateau. Similar to previous studies of subsequent CNS tumors in childhood cancer survivor cohorts, gliomas tended to have a shorter latency (median time from primary cancer, 9 years) than meningiomas (median time from primary cancer, 17 years). After adjustment for radiation dose, primary cancer diagnosis and treatment with chemotherapy did not influence risk of subsequent CNS tumor. These findings confirmed that radiation was the most important risk factor for the development of subsequent CNS tumors in survivors of childhood cancer. Study results also underscored the need for prolonged follow-up of survivors treated with CNS radiation to facilitate early detection of CNS tumors.

Sarcoma

CCSS investigators undertook the first comprehensive evaluation of risk factors for secondary sarcomas in a large cohort of childhood cancer survivors.[38] Previous studies had primarily focused on the role of radiation in the development of sarcoma, whereas associations between secondary sarcoma and chemotherapy—age at treatment and family history of cancer—had not been as well studied.[53,54] The risk of sarcoma was more than nine-fold higher among childhood cancer survivors than among the general population (SIR = 9.02, 95% CI, 7.44 to 10.93). Treatment factors predicting increased risk by multivariable modeling included primary cancer treatment with radiation (RR = 3.1, 95% CI, 1.5 to 6.2), higher doses of anthracyclines (RR = 2.3, 95% CI, 1.2 to 4.3) or alkylating agents (RR = 2.2, 95% CI, 1.1 to 4.6). Survivors with a history of primary sarcoma also exhibited an excess risk of subsequent sarcomas, even after controlling for treatment with radiation and chemotherapy (RR = 10.1, 95% CI, 4.7 to 21.8). This observation, as well as excess sarcoma risk in survivors with a history of other subsequent neoplasms and a family history of cancer, suggested an increased familial risk for carcinogenesis. Study findings are important for identifying survivors with heightened radiation sensitivity who may be targeted for future studies of chemoprevention strategies.

Skin Cancer

Nonmelanoma skin cancer (NMSC) represents one of the most frequent SNs reported by survivors of childhood cancer, but has received little attention in previous publications because these cancers are rarely life-threatening. However, the cumulative morbidity associated with these lesions, which are often multiple in occurrence, prompted CCSS investigators to evaluate the prevalence of NMSC in members of the cohort, its association with RT, and modulators of NMSC risk.[43] NMSC, predominantly basal cell carcinoma, comprised the most commonly occurring type of SN in the cohort and exhibited a strong association with a previous history of RT: 90% of survivors with NMSC had received RT, and 90% of lesions developed within the RT treatment field. The risk of NMSC in survivors treated with RT for primary childhood malignancy was increased more than six-fold (RR = 6.3, 95% CI ,3.5 to 11.3) compared with survivors who did not receive radiation. Study findings underscore the role of RT in accelerating skin cancer induction and the importance of adherence to sun protection behaviors by childhood cancer survivors.

Other Carcinomas

Unlike second primary carcinomas involving the breast, thyroid, and skin, subsequent carcinomas arising in other locations have not been as well characterized in cohorts of childhood cancer survivors. Previous studies reported that treatment for childhood cancer increased the risk of carcinoma involving the parotid gland,[49,51,55-57] lungs,[58-62] gastrointestinal tract,[58-64] and genitourinary tract.[47,51,61,62,65] Extended follow-up of CCSS participants permitted the first evaluation of other adult-onset carcinomas in a large cohort of well-characterized childhood cancer survivors. The risk of

these carcinomas was fourfold (SIR = 4.0; 95% CI, 3.1 to 5.1) higher than that reported by the Surveillance, Epidemiology, and End Results registry; median age at carcinoma diagnosis was much younger than in the general population in whom carcinoma diagnosis is unusual before the age of 40 years.[36] Primary cancer diagnosis significantly influenced the risk for specific carcinoma histology (see Table 4). While the association of increased risk of renal cell carcinoma in survivors of neuroblastoma had been previously described, the excess risk of colorectal and other gastrointestinal cancers after Wilms' tumor represented a novel finding.

Treatment with specific chemotherapeutic agents predicted higher risk of carcinomas in particular locations. Survivors treated with epipodophyllotoxins (SIR = 73.4 *v* 1.8 in unexposed) and alkylating agents (SIR = 7.0 *v* 0 in unexposed) exhibited a greater risk of lung carcinoma compared with those who did not receive these agents. The risk of subsequent colorectal (SIR = 14.7) and kidney (SIR = 48.7) carcinoma was also increased in survivors treated with platinum therapy compared with those who did not receive such treatment. RT resulted in an increased risk of all carcinomas except those of the reproductive tract, with the greatest SIR for subsequent head and neck carcinoma (SIR = 18.5, 95% CI, 12.1 to 28.4). However, nearly one third of carcinomas developed in individuals who were not treated with radiation or in sites distant from RT treatment fields, which suggests that other factors influence carcinogenesis. An important consideration in regards to long-term follow-up of at risk survivors is the latency from primary childhood malignancy to subsequent carcinoma (median, 15 years; range, 6 to 28 years).

Table 4. Unadjusted SIRs and 95% CIs of Subsequent Carcinoma by Primary Diagnosis Group

Carcinoma Site	SIR	95% CI
Leukemia		
Head and neck	20.9	10.5 to 41.8
Bladder	10.6	2.7 to 42.3
Soft tissue sarcoma		
Head and neck	21.6	8.1 to 57.6
CNS tumor		
Head and neck	10.1	2.5 to 40.3
Kidney	11.3	1.6 to 80.0
Hodgkin's disease		
Head and neck	12.3	5.5 to 27.4
GI, excluding colon/rectum	7.4	2.8 to 19.6
Lung	6.6	2.1 to 20.5
Non-Hodgkin's lymphoma		
Head and neck	11.8	2.9 to 46
Male genitourinary	14.5	2.0 to 102.7
Bladder	9.6	1.4 to 68.4
Wilms tumor		
Colon and rectum	25.4	6.3 to 101.4
GI, excluding colon/rectum	18.0	2.5 to 127.6
Neuroblastoma		
Head and neck	20.9	2.9 to 148.2
Female genitourinary	19.1	6.2 to 59.1
Renal cell	329	137 to 791
Soft tissue sarcoma		
Head and neck	21.6	8.1 to 57.6
Female genitourinary	3.8	1.2 to 11.8
Male genitourinary	16.6	2.3 to 118
Bladder	19.8	2.0 to 79.1
Bone tumor		
GI, excluding colon/rectum	7.8	2.0 to 31.2
Kidney	8.0	1.1 to 56.8

NOTE. Excluding carcinomas of the breast, thyroid, and skin, and excluding carcinoma-in-situ.
Abbreviation: SIR, standardized incidence ratios.

Implications for Risk-Based Screening for Subsequent Neoplasms

SNs reported in survivors of childhood cancer range in spectrum from benign and low-grade tumors to high-grade malignancies. The CCSS cohort's large size and extended follow-up has permitted more precise estimates to date of risk and frequencies of subsequent cancers in survivors of childhood cancer than previously published single institution reports, particularly for benign and low-grade tumors that increase in prevalence with longer elapsed time from diagnosis and treatment. The most prevalent SNs observed in childhood cancer survivors include common adult histological subtypes that involve the breast, thyroid, CNS, soft tissues, bones, and skin.[41] Education of childhood cancer survivors and their primary care providers about the risk of SN is important since the age at presentation is typically younger than that observed in individuals who have not had childhood cancer. With the exception of a few histological SN subtypes, risk-based monitoring emphasizes thorough clinical history and physical examination, particularly with attention to organs and tissues in the RT treatment fields. Attention to health behaviors that influence risk of carcinogenesis in the general population should be emphasized as methods of potential risk reduction. Foremost among these is abstinence from tobacco use. Avoidance of excessive sun exposure and adherence to sun protection measures are important to reduce the risk of NMSC.

Breast cancer risk after chest radiation for childhood cancer begins to increase within 8 years following treatment and a substantial proportion of these women will be diagnosed with breast cancer before 40 years of age.[39] Initiating breast cancer surveillance at an early age is anticipated to improve outcomes and reduce mortality among this group. Current recommendations include annual screening mammography with adjunct breast MRI, starting at age 25, or at 8 years after completion of RT, whichever occurs last. In addition, yearly clinical breast examination beginning at puberty until age 25 and then every 6 months is recommended. Survivor education regarding lifestyle factors that influence breast cancer risk, like dietary fat intake, regular physical activity, and alcohol consumption, provides information pertinent to risk reduction.

Reports of gastrointestinal malignancies in cohorts of long-term survivors suggest that radiation likely increases risk, but the median age of onset is not as well established as that of secondary breast cancer following chest radiation. Because early onset of screening may be beneficial for those at highest risk (abdominal, pelvic, and/or spinal radiation $\geq$ 30 Gy), the current recommendation is to initiate surveillance with colonoscopy at age 35 years, or 10 years postradiation, whichever occurs last. Information from the first colonoscopy should inform the frequency of follow-up testing.

CONCLUSION

Childhood cancer survivors may experience complications related to cancer and its treatment that adversely affect quality of life and increase the risk of premature death. Therefore, investigation of health

outcomes after childhood cancer is essential to accurately characterize the impact of cancer-related morbidity on health in adulthood. Previous studies have described a range of physical and psychosocial effects in childhood cancer survivors that have been translated into therapeutic modifications, health counseling and health surveillance recommendations and health preserving interventions across the cancer continuum from diagnosis to long-term survival. Among these studies, CCSS investigations have been particularly noteworthy as they have clarified risk for morbidity in relation to specific treatment modalities and cumulative dose exposures as well as survivor sociodemographic factors. Novel CCSS investigations have also explored the contribution of genetic factors to specific treatment complications. Consequently, these studies more accurately characterize survivors at high risk for cancer-related morbidity who deserve heightened surveillance to optimize outcomes after childhood cancer. Continued study of this cohort will provide the opportunity to more thoroughly evaluate the impact of aging, lifestyle factors, and genetics on long-term health after childhood cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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